IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant:	Robert C. SHIPMAN *et al.*
Title:	Materials and Methods for Analysis of ATP-Binding Cassette Transporter Gene Expression
Appl. No.:	10/582,982
International Filing Date:	December 15, 2004
§ 371(c) Date:	June 15, 2006
Examiner:	Steven C. Pohnert
Art Unit:	1634
Confirmation Number:	1560

REPLY BRIEF

Mail Stop Appeal Brief - Patents
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Sir:

Appellants submit this Reply Brief to address the new issues raised in the Examiner's Answer mailed February 4, 2010.

This Reply Brief is accompanied by a Request for Oral Hearing and the required fee. If this payment is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any overpayment) to deposit account no. 19-0741.

I. ARGUMENT

The Examiner's Answer makes a number of statements, arguments and conclusions already addressed in the Appeal Brief. Appellants focus this reply on the new arguments and issues raised in the Examiner's Answer. Any statements, arguments and conclusions already addressed in the Appeal Brief, but not addressed again here, should not be deemed to be admitted or waived. Moreover, to the extent that any of the Examiner's statements, arguments and conclusions are inconsistent with Appellants' position of non-obviousness as set forth in the Appeal Brief and this Reply, they also should not be deemed to be admitted or waived, even if not individually addressed.

A. Interpretation of the Transitional Term "Having"

At page 9, the Examiner asserts that the transitional term "having" should be construed as open, because there is no specific "limiting definition of 'having'" in the specification, and so "the broadest reasonable interpretation is 'comprising' or open language." In reply, Appellants point out that the Examiner's position in effect creates a default rule that "having" will be construed as open, unless defined otherwise. This position is not supported by the MPEP or the cited case law, which make clear that a case-by-case determination of the intended meaning is required.

Moreover, the Examiner's position ignores the plain language of claim 49 which recites "wherein at least two of the nucleic acid molecules have a nucleic acid sequence consisting of SEQ ID NO:12, 15, 21, 22, 23, 24, 25, 26, 35 or 44." Indeed, the Federal Circuit, in the *Regents of the Univ. of Cal. v. Eli Lilly & Co* case cited by the Examiner, states that claims to a DNA vector which contain the terms "having" and "consisting essentially of" were limited by the "consisting essentially of" language to exclude the presence of other sequences:

> "A DNA transfer vector comprising a [DNA] sequence coding for human [PI] consisting essentially of a plus strand having the sequence . . . ." (emphasis added). The examiner allowed these claims, noting that the required "consisting essentially of" language

> "excludes from the cDNA the presence of sequences other than [those coding for PI]. We agree with the district court that UC thus narrowed its claims in response to a prior art rejection to exclude the materials producing a fusion protein."

Regents at 1573. Thus, the Examiner's interpretation of the transitional phrase "having" is not supported by the MPEP, governing case law, or the context of the instant specification and claims.

B. The Examiner Misapplies the Doctrine of "Equivalence"

At page 22, the Examiner's Answer states that "the instant rejection is not based on the obvious to try rationale, but based on substitution of functional equivalents." In reply, Appellants emphasize that the Examiner has misapplied the doctrine of functional equivalents, and has confounded his analysis with principles from means-plus-function "equivalence" that have no applicability here.

The Examiner alleges that "[n]either the brief nor previous responses have shown that the prior art or specification demonstrate non-equivalence of probes based on the prior art knowledge of the full length sequences." Examiner's Answer at 13. The Examiner cites MPEP § 2183, stating that the section "directs applicants that non-equivalence can be shown by the specification teaching the prior art is not an equivalent, a teaching of the prior art reference itself showing non-equivalence, or a declaration under 37 CFR1.132 showing evidence of non-equivalence." *Id.*; *see also* Examiner's Answer at 14-15.

In reply, Appellants note that "equivalence" as discussed in MPEP § 2183 relates to "means-plus-function" claim limitations. The claims presently on appeal are not means-plus-function claims. Indeed, MPEP § 2183 states that one requirement for a *prima facie* case of equivalence is that "the examiner finds that a prior art element …(c) is an equivalent of the means- (or step-) plus-function limitation." As the claims on appeal do not include any "means-plus-function" or "step-plus-function" claim limitations, this section of the MPEP simply does not apply.

The misapplication of MPEP § 2183 leads the Examiner to improperly shift the burden to Appellants to provide "evidence" that the prior art full-length sequences could not work in the context of the present invention. *See, e.g.,* Examiner's Answer, pages 12 and 14-15. Thus, the Examiner improperly refuses to consider Appellants explanations on point, because they are "arguments of counsel" that "have not been substantiated by evidence . . . that the full length sequences could not work." Appellants maintain that the Examiner's requirement for evidence of non-equivalence is misplaced, and that this basis for the rejection is legally incorrect.

C. There is No "Functional Equivalence" To Full-Length Probes

Throughout the Examiner's Answer, the Examiner asserts that the claimed arrays based on specific sequences are *per se* obvious over the full-length sequences "absent secondary considerations." *See, e.g.*, Examiner's Answer, pages 6 (last paragraph), 7 (last paragraph), page 10 (first paragraph), page 13 (first paragraph), page 14 (last paragraph), page 16 (middle), page 17 (last paragraph). In reply, Appellants emphasize that the doctrine of functional equivalence does not apply here, where there is no prior art array that could be functionally equivalent to the claimed arrays. Moreover, the Examiner has provided no evidence or reasoning as to how an array based on full-length sequences could be functionally equivalent to the claimed arrays, which uniquely identify specific ABC transporter genes.

Appellants have explained that the claimed sequences uniquely identify different ABC transporter genes, i.e., each probe specifically hybridizes to only one of the 48 known genes. This also is stated in the Shipman Declaration, in paragraph 8. At page 11, the Examiner's Answer dismisses this aspect of the claimed invention, because "the claims are drawn to a product of an array and thus are examined by their structural features not their intended use." In reply, Appellants emphasize that the ability to uniquely identify different ABC transporter genes is a characteristic of the claimed product, and is directly relevant to the question of whether an array based on full-length sequences could possibly be functionally equivalent to the claimed arrays. The Examiner's assertion that the function of the claimed arrays is irrelevant to patentability is wholly inconsistent with the rejection based on functional equivalence.

At page 12, the Examiner further dismisses this point because the claims do not specify that the probes hybridize to only a single nucleic acid, because the specification defines "specifically hybridizes" in terms that do not exclude all possible cross-hybridization, and because the claims do not specify hybridization conditions. *See also* Examiner's Answer, page 15. In reply, Appellants point out that the claims do not need to further characterize the recited probes because the probes are fully defined by their nucleotide sequences. Again, as stated in paragraph 8 of the Shipman declaration, the recited probes "each specifically hybridize to one ABC transporter gene." This specificity is due to the hybridization properties of the specifically recited nucleotide sequences, and does not need to be expressly recited or further qualified in the claims.

At page 12, the Examiner's Answer states that an array comprising any ABC transporter gene probe would specifically hybridize to only one ABC transporter gene if only one ABC transporter gene were present in the sample. In reply, Appellants explain that in such a case, only one of Appellants' probes would hybridize with the target sequence. In contrast, if an array were used that included probes that do not uniquely identify the different ABC transporter genes, multiple probes would hybridize with the target sequence. Thus, while the use of the claimed arrays would permit the skilled artisan to identify which ABC transporter gene was present, a different array at best would inform the skilled artisan that an ABC transporter gene is present, but would not provide any information as to which one of the 48 known genes it is. Thus, even in the Examiner's example, the present invention would provide an important and distinct advantage over an array based on full-length sequences, and so would not be functionally equivalent.

D. The References Provide No Guidance To Make An Array As Claimed

Throughout the Examiner's Answer, the Examiner states that "Denefle suggests the making of microarrays, thus rendering obvious to one of skill in the art making a microarray to detect ABC transporter gene expression." Examiner's Answer at 11; *see also id.* at 10, 12, 19 and 21. In reply, Appellants emphasize that the claims on appeal are drawn to not just any ABC transporter gene array, but to arrays comprising specific ABC probe sequences which are not described or suggested in the art cited. *Cf.* Examiner's Answer at 19, 21.

The Examiner maintains that he has "provided specific sequences and motivation to combine them in an array, and that "[t]here is no evidence that the combined teachings result in anything more then the predictable use of prior art elements according to their established function." Examiner's Answer at 14; *see* also *id.* at 19. However, this synopsis ignores the fact that the cited sequences are full-length sequences, and ignores Appellants' statements and evidence regarding the non-obviousness of the specific probe sequences recited in the claims.

Throughout the Examiner's Answer, and at page 14 for example, the Examiner asserts that Denefle teaches probes that would function to detect ABC transporter genes. In reply, Appellants emphasize that Denefle does not teach any specific probes that could uniquely identify any one specific ABC transporter gene. Denefle merely states that probes may consist or comprise 12-1500 consecutive bases of any one of its full-length sequences or of a complementary sequence. Denefle, page 61. Denefle does not provide any suggestion or guidance to design probes that each uniquely identify a single ABC transporter gene, as recited in the claims. Thus, the claimed arrays are more than the combination of prior art elements for use in their established function, because it is only Appellants, and not the prior art, who have taught probes that each uniquely identify one ABC transporter gene, and so can be used in the new and non-obvious function of identifying which of the 48 known ABC transporter genes are present in a sample.

At page 21, the Examiner's Answer dismisses Appellants' explanation of the number of possible probes that theoretically could be based on the 48 known ABC transporter genes and selected for use in a microarray. *See* Appeal Brief at 21 ("Even if there were only 10 possible probes for each gene, that would result in 1×10^{48} possible arrays. Focusing on the 10 probes recited in the claims, and assuming only 10 possible probes for each gene, the claimed array is still 1 out of a possible 10,000,000,000."). The Examiner states that this argument is not persuasive "as the instant rejection is not based on the obvious to try rationale, but based on substitution of functional equivalents." Examiner's Answer at 22. The Examiner also alleges that "the arguments are beyond the scope of the claimed invention" because claim 49 recites only two or more probes and claim 78 recites 10 probes, not probes to all 48 genes." *Id.*; *see also* Examiner's Answer at 11.

In reply, Appellants explain that this point indeed is relevant to the claims on appeal, because it explains the numerous probes that could be selected from the prior art full-length sequences, in contrast to the very specific sequences that are recited in the claims. Moreover, because the claims are open-ended with regard to the number of probes that can be present, the possible number of probes for each of the 48 genes is a pertinent factor when evaluating the claims for non-obviousness. Thus, Appellants' statements are not beyond the scope of the claimed invention.

E. The Examiner Incorrectly Distinguishes the Cited Board Decisions

At pages 13-17, the Examiner's Answer incorrectly distinguishes and improperly dismisses the non-precedential Board decisions cited in the Appeal Brief for information and guidance.

For example, the Examiner states that "[i]n Ex parte Kolberg there is evidence of an unexpected resulted [*sic*]" and so ignores the case for this reason. Examiner's Answer at 13-14. However, in *Kolberg*, the Board held that "[h]aving concluded that the examiner has not established a prima facie case of obviousness, we do not reach the rebuttal declaratory evidence." *Kolberg*, slip op. at 10. Thus, the evidence of unexpected results was not even considered in the cited Board decision, and so is not a valid basis for distinction.

At page 14, the Examiner alleges that *In re O'Farrell* and *In re Kubin* are not relevant because "the examiner has provided specific sequences and motivation to combine them in an array." In reply, Appellants emphasize that the Examiner has not cited a prior art disclosure of any of the specific sequences recited in the claims, or any other sequences that perform the same function of uniquely identifying the different ABC transporter genes. Thus, *In re O'Farrell* and *In re Kubin* are directly on point, because the rejection here "merely throws metaphorical darts at a board filled with . . . prior art possibilities" without even a target or bull's eye to lead to the present invention.

At pages 15-17, the Examiner distinguishes *Ex parte Weichselbaum*, alleging that the "ambiguity" at issue in that case is not found here, because "substitution or addition of the sequences taught by [the cited references] in the arrays taught by Denefle would produce a

microarray with probes equivalent to the recited SEQ ID NO by replacing or adding known ABC transporter gene sequences for another." Examiner's Answer at 16-17. However, the "ambiguity" discussed in *Weichselbaum* is extremely relevant here, as the Examiner has provided no evidence or reasoning showing that the full-length sequences disclosed in the cited art would be equivalent to the claimed sequences, when used on an array as claimed.

Thus, Appellants maintain that the cited Board decisions provide helpful guidance and are informative here, and support Appellants' position of non-obviousness.

F. Declaration of Dr. Robert Shipman Under 37 CFR § 1.132

Throughout the Examiner's Answer, the Examiner asserts that Appellants have not provided any "evidence" to support their positions. In reply, Appellants point to the Shipman Declaration, which provides direct evidence on several issues raised by the Examiner.

At page 8, for example, the Examiner's Answer states that "the declaration does not demonstrate an unexpected result or secondary consideration." In reply, Appellants point to paragraph 8, which attests to the unique properties of the recited probes, and paragraphs 18-22 (and the related data) which discuss the advantages that the claimed probes have over probes designed from full-length sequences using PCR primer design software.

At page 13, for Example, and again at page 14, the Examiner's Answer alleges that Appellants have not shown evidence of non-equivalence. In reply, Appellants emphasize that the Examiner improperly shifted the burden to Appellants, because no *prima facie* case of obviousness has been established. Moreover, Appellants note that the Shipman declaration provides evidence of non-equivalence, by demonstrating that probes designed from full-length sequences using PCR primer design software were not equivalent to the recited probes. Shipman Declaration, paragraphs 18 and 22.

Throughout the Examiner's Answer, for example at pages 7, 13 and 15, the Examiner states that the declaration "is drawn to methods of selecting the probes and has not provided any evidence that the probes derived from the known sequences would not function in an equivalent fashion to those claimed." This is not correct. The Shipman Declaration, in

paragraphs 18 and 22, plainly attests that probes designed from full-length sequences using available PCR primer design software are not equivalent to the claimed probes. Moreover, in response to the Examiner's criticism that the declaration discusses methods of selecting probes, Appellants note that this evidence is directly responsive to assertions made during prosecution and repeated at pages 5-7, and 16-17, for example, that "[d]esigning probes . . . is routine experimentation," that "many internet websites" provide free software for this process, and that the skilled artisan would "have a reasonable expectation of success of obtaining additional probes from the known sequences." The Shipman Declaration attests that the only software known to Dr. Shipman relates to the design of PCR primers, and that "the prior art does not teach the necessary information that would allow a person skilled in the art to identify probe sequences" as recited in the claims. Shipman Declaration, paragraph 15. The Declaration demonstrates this, showing that probes designed from full-length sequences using PCR primer design software are not equivalent to those described and claimed by Appellants. Shipman Declaration, paragraphs 16-18. Thus, the Declaration evidences that designing probes to uniquely identify different ABC transporter genes is an unpredictable undertaking. *See, e.g.*, Shipman Declaration, paragraphs 18-22.

At page 20, the Examiner's Answer states in reference to the Shipman Declaration that "applicant has asserted that the claims have improved results based on in silico analysis . . . while noting that the in silico analysis is not predictable." Appellants assume that the Examiner is referring to the discussion of the BLAST analysis in paragraphs 17 and 18 of the Declaration on the one hand, and the discussion of the unpredictability of the selectivity of in silico-designed primers in paragraph 19 on the other hand. There is no inconsistency between these points. The BLAST scores (which are based on sequence homology with the target sequence) are sufficient to show that the claimed probes will be better probes for the target sequences than the software-designed probes. The point in paragraph 19 is that even PCR primers that are designed to produce a single PCR product may, in actual use, generate multiple PCR products. Thus, further testing of software-designed probes is required to confirm selectivity. This underscores the difficulty and unpredictability of designing probes that uniquely identify only one out of a related family of genes. Thus, the Shipman Declaration provides direct evidence in support of non-obviousness.

G. Consideration of Appellants' Arguments

In several places, such as at pages 9 and 14, the Examiner's Answer refuses to consider Appellants' arguments because they are not supported by "evidence." Although the Examiner's Answer cites MPEP 716.01(c) for the specific types of attorney statements that must be supported by evidence (unexpected results, commercial success, etc.) the Examiner's Answer improperly applies this requirement to Appellants' explanations of different issues.

For example, the Examiner's Answer refuses to consider Appellants' point that full-length sequences comprising thousands or tens of thousands of nucleotide bases would not be suitable for use as probes on an array because of their length and likely regions of homology, which would lead to false positive signals. This explanation is based on basic scientific principles of hybridization and homology, and should not require an affidavit for consideration. Moreover, these statements are founded on teachings in the specification, because all of the claimed sequences and all of the sequences disclosed in the specification for use as probes in an array are less than 900 nucleotides in length, and that none of the examples of sequences to be used in an array include full-length ABC transporter genes.

At page 9, the Examiner's Answer alleges that this point is inconsistent with Denefle's teaching that probes with lengths of 1000 to 1500 nucleotide bases can be used. In reply, Appellants point out that Denefle's teaching of 1000-1500 base probes does not undermine Appellants' point that nucleotides comprising thousands or tens of thousands of bases (such as the cited full-length sequences) would not be suitable.

CONCLUSION

Thus, for these reasons and those already set forth in the Appeal Brief, the pending rejections should be reversed.

Respectfully submitted,

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